

Respiratory Food Allergy

A variety of respiratory tract symptoms may be attributed to, or associated with, food allergy. The role of food in causing respiratory allergies is probably underestimated. Food-induced upper and lower respiratory tract disorders seem to be more common in infants and young children than in adults.¹⁻⁴ However, there is an erroneously inflated public perception of food allergy-induced asthma that often is not substantiated by food challenges.^{5,6}

The incidence of food-triggered wheezing was noted in 2% to 8% of both children and adults with asthma.^{7,8} Food allergy might be considered in patients who have chronic respiratory symptoms that are otherwise unexplained and do not respond adequately to the usual therapeutic measures.⁹ A questionnaire-based study conducted on 33,110 people in France estimated that 3.24% of the French people have food allergy and that the main manifestations were atopic dermatitis for children younger than 6, asthma for those between ages 4 and 6, and anaphylaxis in adults older than 30.¹⁰ In another recent investigation, asthma and allergic rhinitis remained significantly associated with food allergy and sensitization to food allergens after adjustment for confounders as well as for sensitization to aeroallergens.¹¹

This article provides practical information on the role of food allergy in the causation or prediction of respiratory tract morbidity. It also outlines



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evidence-based indications to evaluate patients with upper or lower respiratory tract symptoms for food allergy.

PATHOGENESIS OF FOOD-INDUCED RESPIRATORY ALLERGIES

Food allergy encompasses a variety of immune-mediated adverse reactions, including immunoglobulin E (IgE)-mediated, cell-mediated, and mixed-mechanism disorders.¹² Immune responses mediated by specific IgE antibodies to food allergens are the most widely recognized mechanisms of food-induced respiratory tract symptoms. The establishment of IgE-bearing cells in the nasal or bronchial mucosa during the allergic sensitization process sets the stage for their activation during subsequent allergen exposure.¹³ IgE-mediated reactions are responsible for allergic rhinoconjunctivitis, bronchospasm, and anaphylaxis that may result from food allergens. Non-IgE-mediated mechanisms are probably involved

in the food-induced chronic pulmonary disease (Heiner syndrome) and the hypersensitivity pneumonitis which results from inhalation of food dust, while bronchial asthma in those with food allergy may result from mixed IgE and cellular components (Sidebar 1).^{1-3,12,14}

Specific food allergens have been implicated in these reactions. The Class I food allergens (ie, milk, egg, seafood, wheat, soy, peanut, and tree nuts) are the most common.^{6,15} Cow's milk is the main cause of Heiner syndrome.¹⁶ In a study of 1,141 randomly selected young adults, those with probable IgE-mediated peanut and shrimp allergy were significantly more likely to have current asthma.¹⁷ Wheeze and history of eczema were also associated with peanut allergy, whereas nasal allergies were associated with shrimp allergy. In another study, a cohort of 1,218 consecutive births was evaluated for the relation between egg allergy and respiratory allergic disease by age 4.¹⁸ The presence of egg allergy in infancy, especially when co-existing with eczema, increased the likelihood of respiratory allergic symptoms and aero-allergen sensitization in early childhood. Another birth cohort from England revealed that skin sensitivity to hen's egg, cow's milk, or both during the first 5 years of life was predictive of asthma.¹⁹ Further evidence for the close association between food and respiratory allergy is derived from the fact that sensitization to pollen proteins can result in allergic reactions to fruits and vegetables (Class II food allergens) with homologous proteins (pollen-food syndrome).¹⁰

A cross-sectional prevalence study from New Zealand on 1,321 children found that frequent consumption of fast foods, especially hamburgers, resulted in a dose-dependent association with asthma symptoms and that frequent "takeaway" consumption showed a similar association with bronchial hyperresponsiveness.²⁰ A high percentage of patients with asthma perceive that food

SIDEBAR 1.

Respiratory Immune-mediated Food Reactions

IgE-mediated Reactions

- Allergic rhinitis
- Bronchial asthma
- Respiratory symptoms of anaphylaxis
- Recurrent secretory otitis media

Non-IgE-mediated Reactions

- Food-induced chronic pulmonary disease (Heiner syndrome)
- Food-induced hypersensitivity pneumonitis

additives (eg, monosodium glutamate) contribute to worsening of their respiratory symptoms; however, well-controlled investigations in this area have reported a prevalence rate below 5%.⁶ Sulfite-containing foods (eg, dried fruits, wines) have been shown to cause bronchospasm and severe asthmatic attacks in some patients.²¹ Reactions to food additives should be suspected in patients who report symptoms to multiple unrelated foods or to a certain food when commercially prepared but not when homemade, and when the allergy evaluation rules out a role for food protein.²²

In addition to ingestion, respiratory food allergy may occur by inhalation or contact with mucous membranes or skin.^{23,24} Asthmatic responses may occur from direct inhalation of aerosolized particles that contain allergenic food. Occupational asthma has been reported in crab-processing workers, bakery workers (due to inhaled egg or flour), and harbor workers unloading soybeans.³ Interestingly, patients with "baker's asthma," caused by inhaled wheat flour, can eat wheat without symptoms.²⁵ In 1990, soy antigen was listed as an agent causing occupational disease when a soybean-dependent asthma epidemic occurred in Barcelona and Cartagena, Spain, after a

CME EDUCATIONAL OBJECTIVES

1. Describe the immune-mediated food-induced reactions that affect the airways.
2. Discuss the clinical manifestations and management of respiratory food allergies.
3. Identify the indications to evaluate patients with upper or lower respiratory tract symptoms for the presence of food allergy.

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soy dust discharge into the air.²⁶ Also, inhalation of lupine flour was reported to cause allergic sensitization and occupational asthma.²⁷

Nonoccupational exposure to fish odors or fumes led to symptoms in 10% of 197 children allergic to fish by ingestion.^{28,29} Some children had symptoms even on direct or indirect skin contact with fish. Sicherer et al.³⁰ reported on a series of people with peanut allergy who experienced adverse respiratory reactions on exposure to peanut dust on airline flights that serve peanut snacks. In another study, symptoms of asthma and rhinitis were reported in three patients after exposure to raw but not cooked green beans and chards in a nonoccupational setting.³¹

Several reports indicate that food sensitization can occur perinatally, leading to reactions on the first exposure. Food antigens can also be excreted by the mammary gland and can sensitize or provoke reactions in exclusively breast-fed infants.²⁴

MILK-INDUCED CHRONIC PULMONARY DISEASE

In 1960, Heiner and Sears³² described a syndrome of recurrent pulmonary infiltrates in a group of seven infants fed with cow's milk who had chronic cough, recurrent fever, tachypnea, wheezing, rales, failure to thrive, and family history of allergy. Four of them also had hemoptysis and anemia due to pulmonary hemosiderosis (PH), as verified by the presence of iron-laden macrophages (ILM) in the bronchial aspirate or morning gastric washing using Prussian blue stain. Sera of all patients demonstrated cow's milk precipitins by slide double immunodiffusion using the micro-Ouchterlony technique.³³ The authors reported that most symptoms decreased within a few days or weeks after cow's milk elimination or switching to heat-treated milk.³²

Heiner syndrome seems to be rare,

but most probably is underdiagnosed due to paucity of its pathognomonic features.¹⁶ Since its discovery, only a few reports have been published.³⁴⁻³⁶ The largest series (eight infants) was reported by Moissidis et al.¹⁶ The infants were fed cow's milk starting at birth, and at ages ranging from 1 to 9 months, they became symptomatic in the form of cough in seven, wheezing in three, hemoptysis in two, nasal congestion in three, dyspnea in one, recurrent otitis media in three, recurrent fever in four, anorexia and gastrointestinal complaints in five, hematochezia in one, and failure to thrive in two. All infants had radiological evidence of pulmonary infiltrates, and the six infants who were tested for precipitating antibodies to cow's milk proteins demonstrated high titres. PH was confirmed in one patient who showed ILM in the bronchoalveolar lavage (BAL), gastric washing, and open lung biopsy. Symptoms improved within

The specific immunologic mechanisms responsible for this syndrome are not clear. It is certainly a non-IgE mediated reaction in which type III hypersensitivity (Arthus reaction) may play a role, leading to the formation of immune complexes that cause inflammation in the alveolar capillaries. When such vasculitis is severe, bleeding ensues, causing PH.^{1,3} Cell-mediated reaction (type IV) also may have a role, as the lymphocytes of some patients demonstrate blast transformation in vitro on exposure to cow's milk protein antigens.³⁸ Often, more than one immunologic mechanism is involved, and perhaps all four types of reactions are involved in certain patients.^{16,39}

Although peripheral blood eosinophilia is commonly observed and serum total IgE is sometimes elevated,^{6,16} their significance is probably limited to the associated atopy in some of those infants. Also, the presence of high titres of precipitating (IgG) antibodies against bovine milk pro-

A high percentage of patients with asthma perceive that food additives (eg, monosodium glutamate) contribute to worsening of their respiratory symptoms.

days of milk elimination, whereas clearing of pulmonary infiltrates took several weeks. Parents consented to milk challenge in only three cases, all of whom developed recurrence of symptoms.

The most allergenic cow's milk components are beta-lactoglobulin and casein, which are heat stable, followed by alpha-lactalbumin and gamma-globulin, which are heat labile. Therefore, patients who are allergic to the latter proteins usually tolerate heat-treated milk.^{16,37} Although cow's milk is the most common cause of Heiner syndrome, a few other foods have been incriminated in older children (eg, soy, egg, and pork).¹⁶

teins, although helpful in the diagnosis, is not pathognomonic of the disease. It can be present in low titres in sera of normal subjects ingesting milk and in high titres in some diseases, such as celiac disease, cystic fibrosis of the pancreas, IgA deficiency, familial dysautonomia, Down syndrome, Wiskott-Aldrich syndrome, and Hurler syndrome.^{40,41}

Gastroesophageal reflux (GER) was documented in one patient in the Moissidis series.¹⁶ Although milk aspiration cannot solely explain all the components of the disease, it would be wise to exclude GER, uncoordinated swallowing disorders, and tracheal or esophageal

Indications to Evaluate Patients With Respiratory Tract Disorders for the Presence of Food Allergy

- History of wheezing or asthma exacerbation triggered by food
- Asthma associated with history of atopic dermatitis or food-induced anaphylaxis
- Recalcitrant and/or severe bronchial asthma, especially in infants and children
- Persistent allergic rhinitis especially if there is history of other food-induced allergies
- Chronic pulmonary symptoms and infiltrates in a cow's milk-fed infant
- Pulmonary hemosiderosis in infants and children if otherwise unexplained
- Chronic respiratory symptoms in subjects occupationally exposed to food dust or fumes

Exclude food allergy in every patient with history of an anaphylactic reaction unless another offending agent is documented

anomalies during the evaluation of infants with suspected Heiner syndrome. An increased incidence of dysfunction of the lower esophageal sphincter was reported in a group of children with recurrent pulmonary disease.⁴²

The diagnosis of Heiner syndrome should be based on the subsequent resolution of symptoms and radiologic findings after milk elimination, supported by the presence of milk precipitins in the serum. Confirmation of the diagnosis would require documentation of recurrence of manifestations following milk challenge. However, most parents are so impressed by the improvement that they refuse the challenge test.^{16,24} In patients who develop the complication of PH, it is necessary to verify the diagnosis by the demonstration of ILM in smears of tracheal aspirates or morning gastric washing fluid. Immunofluorescence studies of lung biopsy specimens may show deposits of immunoglobulins, complement, fibrin, and milk protein antigens diffusely scattered throughout the lung tissue.³⁵ Cow's milk-induced PH should be differentiated from idiopathic primary PH by the better prognosis of the former after cow's milk elimination and the fulminant course of the latter that requires long courses of corticosteroids and other

aggressive immunomodulatory therapies.¹⁶ Without treatment, idiopathic primary PH leads to progressive pulmonary fibrosis and eventually death.⁴³

Treatment of Heiner syndrome is strict avoidance of cow's milk or any other identified offending food. Infants may be given a milk substitute such as soybean formula, extensively hydrolyzed protein formula, or an elemental diet of synthesized amino acids.¹⁶ Parents or caregivers are encouraged to carefully inspect the food labels for their content; food labeling laws effective in the United States since January 2006 require simple terms to indicate the presence of a major food allergen (eg, milk instead of casein).

Symptomatic treatment initially is needed (eg, bronchodilators, antihistamines, systemic or inhaled corticosteroids, and in some cases iron therapy). In PH, corticosteroids and, in severe cases, immunosuppressants are sometimes indicated.¹⁶ Cyclophosphamide was successfully used in a refractory case of cow's milk-induced PH.⁴⁵

The prognosis is generally good if a milk-free diet is begun early. An early diagnosis is therefore mandatory and this requires sufficient awareness of its clinical presentations. Many patients will tolerate cow's milk within a few years.¹⁶

FOOD ALLERGY AND ASTHMA

The incidence of food allergy in children with asthma (6% to 8%) is lower than that in atopic eczema (35%), but when a child has both asthma and atopic eczema, the likelihood of food allergy rises.^{2,6,46} Additionally, considerable epidemiological data suggest a link between asthma and food allergy.⁴⁷ Food can induce bronchospasm, and food allergy has been implicated as a risk factor for life-threatening asthma. Asthma also seems to be a risk factor for life-threatening food allergy.^{4,47,48} The mechanism underlying this connection is unclear, but the co-existence of food allergy should be considered in any child with asthma, especially if there is history of atopic dermatitis, elevated serum IgE level, or both.^{47,49} Eosinophilia in the sputum of food allergy patients was considered predictive of respiratory involvement in a recent investigation.⁵⁰

Food-induced asthma is observed during systemic allergic reactions to food. Screening for food allergy in 140 children with asthma by clinical history and specific IgE antibodies, followed by blinded food challenge in 32 positive, cases showed that 9.2% had food-induced respiratory symptoms and 5.7% had specific asthmatic reactions.⁵¹ Food-induced bronchospasm was reported in 8.5% of 284 children with asthma in whom hen's egg constituted the most frequent causative agent, especially during the first year of life.⁵²

Businco et al.⁴⁹ reported that 11 out of 42 children with atopic dermatitis and cow's milk allergy developed asthmatic symptoms during a positive challenge and that in six children, asthma exacerbation was the only adverse symptom observed. Another investigation revealed that 29% of children with IgE-mediated cow's milk allergy experienced lower airway responses on oral challenge compared with 4% in children with non-IgE-mediated gastrointestinal allergy to cow's milk. A third group with

late-onset reactions to oral cow's milk challenge were suffering from chronic asthma or atopic dermatitis; 50% of them experienced wheezing after the milk challenge.⁵³

A study from Taiwan revealed that 33 of 88 children with elevated specific IgE levels to only food allergens met the diagnostic criteria of asthma. The most common food allergens were milk and egg white.⁵⁴ Likewise, an investigation from Turkey confirmed that food allergy can elicit asthma in children younger than 6, but the incidence was low, even for major food allergens such as egg and cow's milk.⁵⁵ A study at John Hopkins Hospital revealed that 34 (17%) of 205 children with positive food challenges developed wheezing as part of their reaction and that 6 of 88 cases who were monitored with pulmonary function tests had a decrease of more than 20% in forced expiratory volume in the first second (FEV₁).⁵⁶

In some patients, the manifestations of food allergy can be limited to subclinical bronchial hyper-reactivity (BHR), which is difficult to recognize.³ In other words, the chronic ingestion of a food to which one is allergic may result in increased BHR despite the absence of acute symptoms on ingestion.⁶ Airway hyperresponsiveness was measured by standardized metacholine inhalation challenges before and 4 hours after food challenge in 26 patients with asthma and food allergy. Significant changes in BHR could be detected in the majority of patients who experienced chest symptoms during a positive challenge.⁵⁷ On the other hand, a placebo-controlled study conducted on a limited number of patients with asthma concluded that food allergy is an unlikely cause of BHR in adults, although the patients gave a history of food-induced wheezing.⁵⁸ Another recent investigation demonstrated BHR in 40% of a group of young adults with food allergy alone and in all patients with concomitant food allergy and asthma.⁵⁰ As a matter of fact, food aller-

gy may coexist with an inhalant allergy and in some instances, food may have a nonspecific role in the preparation of bronchi for the possible consequent stimulus.⁵¹ Mite sensitivity in patients with food allergy was predictive for respiratory allergy in one series.⁵⁰

FOOD ALLERGY AND THE UPPER AIRWAY

Rhinitis induced by oral food challenges is more frequently observed in infants and young children than in adults.⁶ It has accounted for 70% of the respiratory symptoms observed in a group of children who underwent double-blind, placebo-controlled food challenge (DBPCFC).⁵⁶ A study on the relationship between food allergy and asthma and allergic rhinitis in schoolchildren demonstrated that allergic rhinitis was more prevalent than asthma, and both were positively associated with food allergy.¹¹ A recent investigation on adults

rhinovirus, milk intake was not associated with increased nasal secretions, symptoms of cough, or nasal congestion.⁶¹ Another investigation using a randomized, crossover, double-blind, placebo-controlled design revealed no statistically significant difference in FEV₁ and peak expiratory flow rate on milk challenge in a group of adults with asthma who believed their symptoms worsened with the ingestion of dairy products.⁶² It seems unlikely that dairy products have a specific negative effect on patients with allergic rhinitis or bronchial asthma, but some infants with IgE-mediated cow's milk allergy may develop asthma.^{6,49,60}

The role of food allergy in otitis media is controversial and probably uncommon. It may occur secondary to other respiratory allergies.^{15,63,64} Allergic inflammation in the nasal mucosa may cause Eustachian tube dysfunction and subsequent otitis media with effusion.^{1,6} It has been suggested that large tonsillar and adenoid

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with seasonal rhinitis revealed that food allergy was the most common (14%) accompanying allergy although the most common clinical manifestations of food allergy in that series were oral allergy syndrome and cutaneous symptoms.⁵⁹ Allergic rhinitis typically occurs in association with other clinical manifestations (eg, cutaneous or gastrointestinal) during acute allergic reactions to food and rarely occurs in isolation.^{15,56}

There is a belief among some patients that the consumption of milk and dairy products increases the production and thickness of mucus in the nose and respiratory system.⁶⁰ In people inoculated with

tissues might be aggravated by food allergy leading to upper airway obstruction.⁹ The middle ear could otherwise be the primary shock organ.^{1,65} It was reported that, in a subset of infants with recurrent otitis media, IgG complexes with cow's milk proteins may contribute to the middle ear inflammation.⁶⁶ However, due to the paucity of available data, routine testing for food allergy in patients with otitis media is not recommended.⁶

RESPIRATORY MANIFESTATIONS OF FOOD-INDUCED ANAPHYLAXIS

Respiratory symptoms are a common and important indicator of severe food-

induced anaphylaxis. These symptoms typically include pruritus in the oropharynx, laryngeal edema, stridor, cough, dyspnea, wheezing, and dysphonia.⁶ Data from a voluntary registry of 5,149 people, mostly children, with peanut allergy, tree nut allergy, or both showed respiratory reactions in 42% and 62% of patients as part of their initial reactions to peanuts and tree nuts, respectively. Registrants with asthma were more likely to

exposure, but it can occur in children and often goes unrecognized.^{71,72} The immunopathogenesis probably involves immune-complex and cell-mediated responses, and the variability of the disease expression suggests that the genetic background of the affected individual or other factors such as concomitant viral infection may have an influence.

Zubeldia et al.¹⁴ described a case of a 45-year-old research agronomist who

lavage fluid with increased CD8 cells and significant reduction in the helper/suppressor cell ratio.^{75,78} Lung biopsy reveals interstitial alveolitis with lymphocyte-macrophage infiltrate.⁷⁵

The treatment of choice is avoidance, including the use of high-efficiency filter masks and indoor particle filters for the ambient air.⁷¹ Corticosteroid therapy can reduce acute symptoms, with variable success. As with most hypersensitivity diseases, early diagnosis provides the best prognosis.⁷²

The chronic ingestion of a food to which one is allergic may result in increased bronchial hyper-reactivity despite the absence of acute symptoms on ingestion.

EVALUATING POTENTIAL RESPIRATORY FOOD ALLERGIES

Sidebar 2 (see page 736) shows some evidence-based indications to evaluate a patient with upper or lower respiratory tract manifestations for the presence of food allergy. These include recalcitrant or otherwise unexplained allergic rhinitis, asthma exacerbations, or both, especially if the medical history reveals that some of the attacks followed the exposure to particular food(s). The likelihood rises if there are associated disorders that may be related to food allergy, such as moderate to severe atopic dermatitis or history of food-induced anaphylaxis. Another example is the presence of chronic or recurrent cough and pulmonary infiltrates in an infant who is being fed cow's milk or exposed to its antigens during weaning or through excretion in maternal breast milk. A history of occupational or nonoccupational exposure to food dust or fumes may indicate that the patient's symptoms or lung infiltrates are manifestations of hypersensitivity to that food.

The allergy evaluation starts with a medical history, including the age of onset, detailed feeding history, and the relationship between symptoms and exposure to different foods, especially milk, egg, seafood, soy, peanut, and tree nuts. The presence of cutaneous or gastrointestinal allergies should be sought in the history and by physical examina-

have severe reactions.⁶⁷ In another report, 63 of 122 children had lower respiratory tract symptoms as part of their reactions to peanut, tree nuts, or both.⁶⁸

Sampson et al.⁶⁹ reported that peanut, tree nuts, egg, and cow's milk were the foods responsible for the most serious respiratory reactions observed in six fatal and seven near-fatal anaphylactic reactions. However, the causal foods may differ by geographical region and local cuisine.⁶ In a study from Italy, seafood was the most frequent cause.⁷⁰ An epidemiologic survey from France revealed that food-induced anaphylactic reactions correlated with the co-intake of alcohol or nonsteroidal anti-inflammatory drugs.¹⁰

FOOD-INDUCED HYPERSENSITIVITY PNEUMONITIS

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is a form of immune-mediated inflammatory lung disease involving the distal portions of the lungs associated with intense or repeated exposure to a variety of finely dispersed organic antigens, some of which can be food particles. It is more common in adults because of occupational

developed HP after many years of exposure to soybean antigens, as confirmed by a challenge test. HP has also been reported from exposure to other food proteins, such as mushroom spores,⁷³ spinach powder,⁷⁴ and corn.⁷⁵ Inhalation of steam, powder, or flour from some legumes also may cause HP, and due to their emulsifying properties, legumes are used as food additives in many manufactured foods.⁷⁶

Patients with HP present with some characteristic features that usually allow a firm diagnosis. These include a history of exposure to inhaled antigens, relief with antigen avoidance, and a recrudescence of symptoms with re-exposure. Symptoms include cough, dyspnea, fever, malaise, and weight loss. Severe presentations such as adult respiratory distress syndrome and chronic fibrosis may occur.⁷² The diagnosis is supported by the combination of ground glass changes and small nodular lesions on computerized tomography scanning and restrictive and obstructive changes on pulmonary function testing.^{71,77} The patients may also have serum precipitating IgG antibodies and lymphocytosis in bronchoalveolar

tion, and other nonallergic causes of the symptoms should be excluded.³

The patient should then be screened by nonspecific tests to support the possibility of allergy (eg, serum total IgE and eosinophilia) and specific tests such as a food/symptom diary, specific serum IgE, and skin-prick testing (SPT).²⁴ The latter should be guided by the history, as a positive skin test response does not necessarily indicate that the food is causal but a negative SPT usually confirms the absence of IgE-mediated allergic reactivity to a certain food.⁴⁴ Also, commercially prepared extracts often are inadequate in the evaluation of allergy to many fruits and vegetables because of the lability of their antigens.⁷⁹ Food-specific IgE testing is valuable when the antibody concentration exceeds the predictive or diagnostic values.^{45,80} However, undetectable levels may still be associated with positive clinical reactions in 10% to 25% of cases.⁸¹ A large wheal size on SPT was considered to add utility to a moderate elevation of specific IgE to egg white in a recent study.⁸²

Food elimination challenge testing is still the gold standard for the diagnosis of food allergy using the DBPCFC technique and to date is the best available test to evaluate non-IgE mediated respiratory food allergies.²⁴ Open or single-blind oral food challenges often are used as a screening tool.⁴⁴

Once the diagnosis is made, avoidance of the offending food would considerably improve the symptoms.⁴⁷ Nutritional support and alertness to a possible acute reaction on accidental exposure are mandatory.¹² Early diagnosis of respiratory food allergies would certainly prevent morbidity and improve the quality of life.

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